Clinical Pharmacology and Drug Development

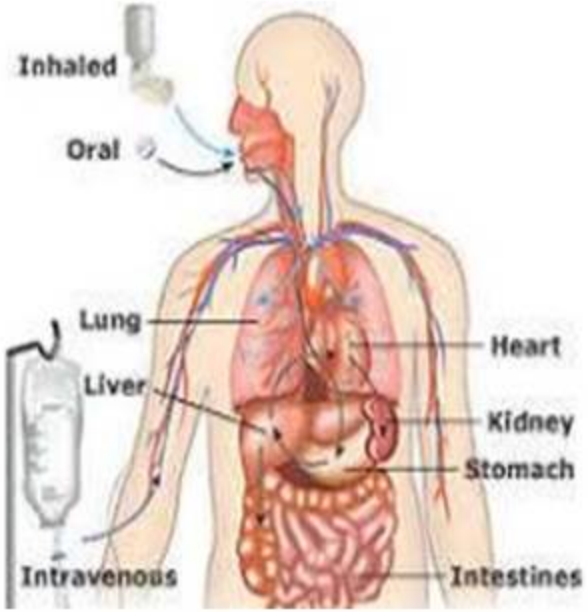
Pharmacokinetics

Module 2 Topic 4

Pharmacokinetics

- **Pharmacokinetics** is the study of the
  - **Absorption**
  - **Distribution**
  - **Metabolism**, and
  - **Excretion** of a drug
- Pharmacokinetics is **what the body does to the drugs**

Pharmacokinetics



The Study of how a drug is absorbed, distributed, metabolized and excreted (known as ADME in the pharmaceutical industry) is called **pharmacokinetics**.

Pharmacokinetics

- **Absorption of a Drug**
  - Process of drug movement from the site of administration towards the systemic blood circulation
  - The way in which a drug is absorbed depends on its route of administration
- Routes of Drug Administration
  - **Enteral** – oral, sublingual, rectal
  - **Parenteral** – injection, inhalation, transdermal
  - **Topical**

Pharmacokinetics

- **Oral Administration**
  - Drugs given by mouth disintegrate and dissolve in the G-I tract and are absorbed into the bloodstream through the intestinal walls
  - Drugs like antacids or laxatives taken by mouth produce a direct effect on the stomach or intestines, respectively
- **Sublingual Administration**
  - Tablet placed below the tongue ('sublingual') results in rapid absorption of the drug into the bloodstream e.g. Isosorbide dinitrate

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- **Rectal Administration**
  - Drugs given in the form of suppositories inserted into the rectum from where they are absorbed into the blood circulation
  - Drugs administered rectally include acetaminophen (for fever), diazepam (for seizures), and laxatives (for constipation)

Pharmacokinetics

Factors that affect the oral absorption of a drug

- Presence of food in the G-I tract
  - Delays absorption of Aspirin, paracetamol, diclofenac
  - Decreases absorption of oral penicillins, erythromycin, tetracyclines
  - Increases absorption of griseofulvin, diazepam
- Time taken for passing of stomach contents into the small intestine ('gastric emptying time')
  - Food, especially fatty food, slows gastric emptying and rate of drug absorption
  - Taking some drugs on an empty stomach speeds absorption
  - Drugs that affect gastric emptying e.g., parasympatholytic drugs affect the absorption rate of other drugs

Pharmacokinetics

Factors that affect the oral absorption of a drug (Contd)

- Time duration for which the drug remains in the intestines
  - Prolonged residence time may increase absorption of Vitamins
- pH of the G-I tract
  - Acidic pH of stomach degrades Penicillin G and erythromycin, hence administered as prodrugs namely carindacillin and erythromycin estolate
  - Acidic drugs (Aspirin) are better absorbed in stomach (in acidic media) and Basic drugs (Diazepum) are better absorbed in intestine (in alkaline media)
- Diseases of the G-I tract
  - Achlorhydria may lead to inhibition of absorption of Vit B_{12}

Pharmacokinetics

- **Administration by Injection**
  - Drugs may be injected into the body to produce a systemic effect
  - One reason for injecting drugs is the rapid response that follows.
  - The main types of injection are
    - Intramuscular
    - Intravenous
    - Subcutaneous

Pharmacokinetics

Administration by Inhalation

- Drugs may be inhaled to produce a systemic effect or a local effect on the respiratory tract
- Drugs administered by nasal route include calcitonin (for osteoporosis), sumatriptan (for migraine headaches)
- Drugs administered by inhalation through the mouth may act specifically on the lungs, such as antiasthmatic drugs like salbutamol
- Gases to produce general anaesthesia are administered by inhalation and are absorbed into the bloodstream through the lungs to produce a general effect on the brain

Pharmacokinetics

Topical Application

- In treating localized disorders such as skin infections and eye / ear infections it is preferable to use drugs in a suitable dosage form so that the drug has a local ('topical') rather than a systemic effect
- For example, artificial tears are used to relieve dry eyes, betaxolol used to treat glaucoma, and those used to dilate pupils, such as phenylephrine and tropicamide produce a local effect after they are absorbed through the cornea and conjunctiva

Pharmacokinetics

Topical Application (Contd)

- Ear drops containing solutions or suspensions are typically applied to the outer ear, little of the drugs enter the bloodstream ; drugs given by the otic route include hydrocortisone, ciprofloxacin, and benzocaine

Pharmacokinetics

Topical Application (Contd)

Cutaneous application

- Drugs applied to the skin usually used for their local effects
- Most commonly used to treat superficial skin disorders, such as
  - Psoriasis e.g. hydrocortisone, betamethasone
  - Eczema e.g. hydrocortisone, dexamethasone
  - Skin infections (viral e.g. acyclovir, bacterial e.g. mupirocin, and fungal e.g. clotrimazole)
  - Itching and dry skin e.g. urea, liquid paraffin
- Depending on the consistency of the inactive substances, the formulation may be an ointment, cream, lotion, solution, powder, or gel

Pharmacokinetics

Topical Application (Contd)

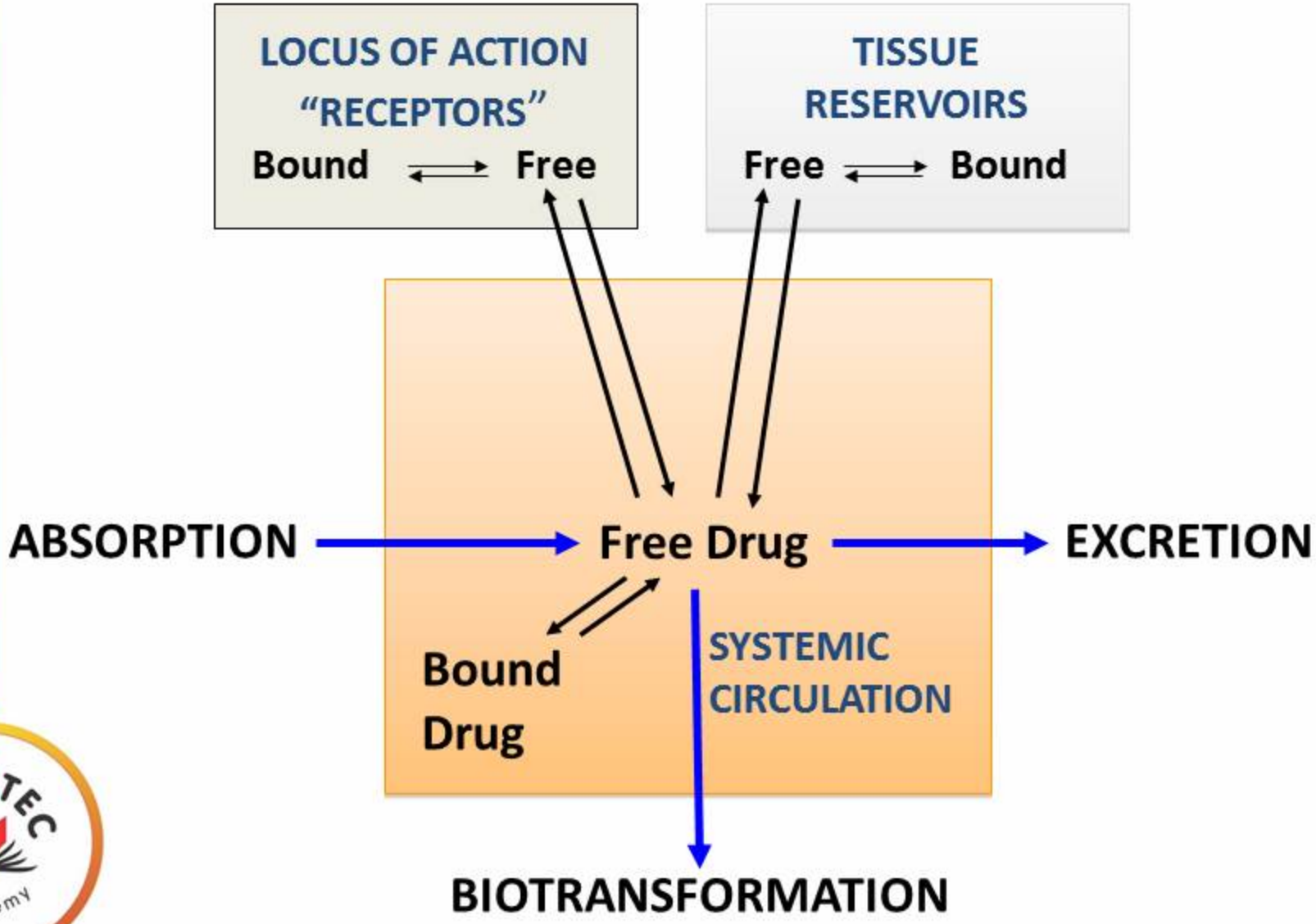
Vaginal route

- Some drugs may be administered vaginally to women as pessaries (vaginal tablets)
- e.g. clotrimazole in the topical treatment of vaginal candidiasis or to give estrogen to women after menopause to relieve vaginal symptoms such as dryness, soreness, and redness

Pharmacokinetics

Distribution of a Drug

- After a drug enters the general circulation it gets distributed throughout the body and passes into various tissues
- Protein Binding - Drugs are transported in the blood partly in solution (as free drug) and partly bound to plasma proteins – mainly albumin
  - Warfarin- 99% bound, Tolbutamide- 98% bound, Phenytoin- 90% bound
  - Free drug is active & gets metabolized & eliminated
  - Bound drug dissociates to replace the drug lost from the body


LOCUS OF ACTION
"RECEPTORS"
Bound ⇄ Free
TISSUE
RESERVOIRS
Free ⇄ Bound
ABSORPTION
Free Drug
EXCRETION
Bound
Drug
SYSTEMIC
CIRCULATION
BIOTRANSFORMATION

Pharmacokinetics

Protein Binding (Contd)

- Displacement interactions where drug bound with higher affinity will displace the one having lower affinity.
  - Phenylbutazone, Salicylates & Sulfonamides displace Tolbutamide → hypoglycemia
  - Salicylates, Indomethacin, Phenytoin & Tolbutamide displace Warfarin → haemorrhage

Pharmacokinetics

Factors affecting Distribution of Drug

- The extent of distribution of a drug in the body depends on many factors, such as:
  - Lipid solubility of the drug e.g. Highly lipid- soluble drugs like thiopentone selectively accumulate in fat and adipose tissue
  - Variations in the pH levels of body tissues i.e. the pH of the blood or tissue affect the ionization of the drug and hence its distribution e.g. 2nd generation antihistamines are ionized molecules at physiological pH that cross the blood-brain barrier poorly compared to first generation antihistamines (uncharged at pH 7.4)

Pharmacokinetics

Factors affecting Distribution of Drug (Contd)

- Protein binding e.g. extensively protein bound drugs like warfarin have smaller apparent volume of distribution
- Permeability of blood vessels e.g. permeability increased in renal capillaries and in specialized hepatic capillaries (sinusoids) resulting in more extensive distribution

- **Blood-brain barrier**
  - Capillaries of the brain lack pores & have connective tissue cells covering around the capillaries (astrocytic sheath)
  - Effectively prevents the passage of drugs and other substances from the blood into the CNS
  - Thiopental is only partly ionized and passes into the brain easily

Pharmacokinetics

Metabolism (Biotransformation) of a Drug

- Metabolism or biotransformation is the process of chemical alteration of drugs in the body
- Metabolism facilitates elimination of the drug from the body
- Most of the drugs are eliminated from the body by the kidneys through the urine.

Pharmacokinetics

- **Reducing Lipid Solubility**
  - Metabolic reactions tend to make a drug molecule progressively more water soluble and less lipid soluble
  - This favours their easier elimination in the urine
- **Alteration of Biological Activity**
  - Most drugs are converted by metabolism from a pharmacologically active to an inactive substance or to another pharmacologically active substance

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Liver is by far the most important organ involved in the metabolism of drugs

- Liver cells contain a number of enzymes that are responsible for many metabolic reactions
- The most important enzyme system of metabolism is cytochrome P-450 (CYP450), a superfamily of isoenzymes that catalyzes the oxidation of many drugs

Pharmacokinetics

For many drugs, metabolism occurs in 2 phases

- Phase I reactions involve formation of a new or modified functional group or cleavage (oxidation, reduction, hydrolysis)
- Phase II reactions involve conjugation with an endogenous substance (e.g., glucuronic acid, sulfate, glycine)
- Metabolites formed in synthetic reactions are more polar and thus more readily excreted by the kidneys (in urine) and the liver (in bile)

Pharmacokinetics

Excretion of a Drug

- Excretion is the process by which a drug is eliminated from the body.
- The major organ responsible for excretion of a drug is the kidney, which eliminates drugs via urine
- Other routes by which drugs are excreted from the body include:
  - Bile
  - Saliva
  - Sweat
  - Breast milk
  - Lungs, etc.

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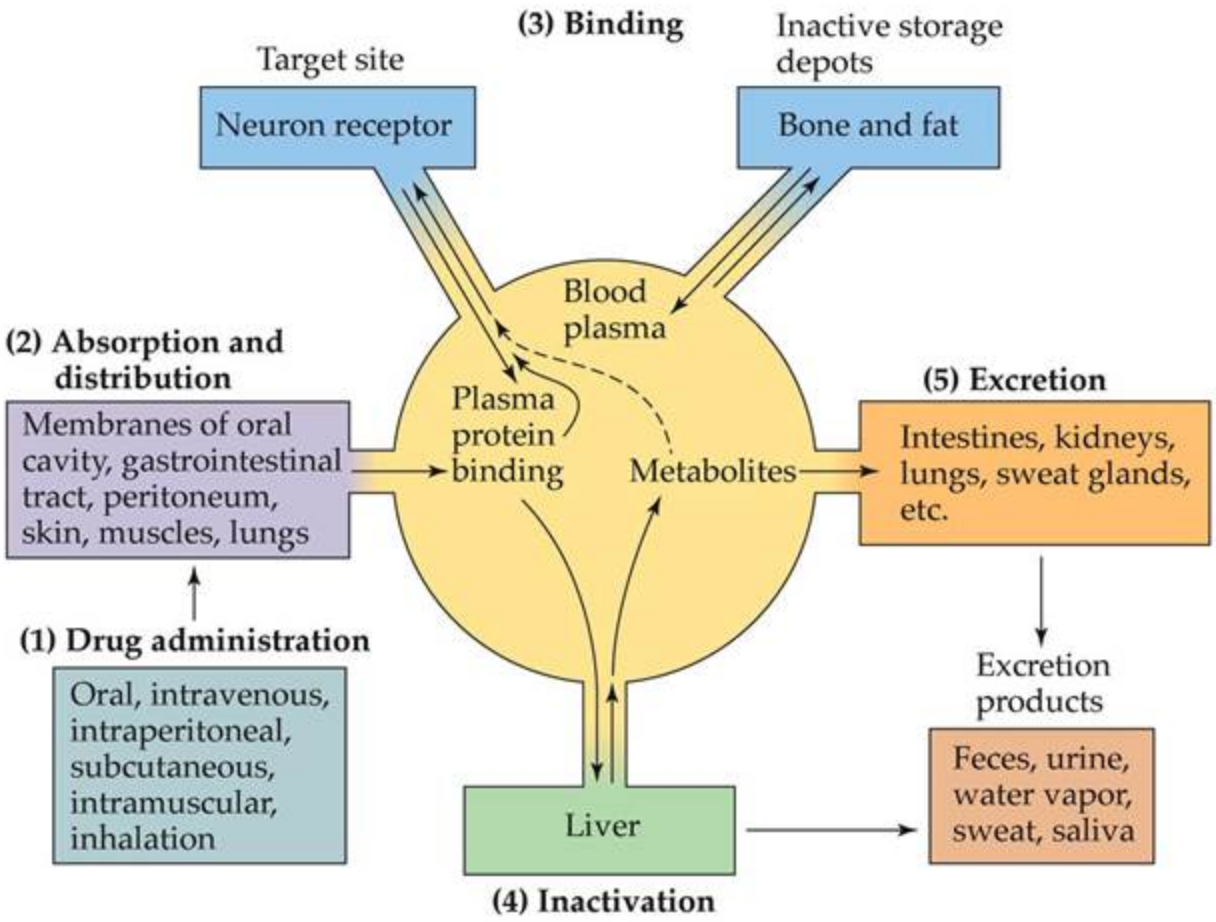


Pharmacokinetics

Bioavailability

- Bioavailability is the rate and extent to which the drug enters the general circulation following administration by oral route

Bioequivalence

- Bioequivalence indicates that the drug products, when given to the same patient in the same dosage regimen, result in equivalent concentrations of drug in plasma and tissues

Pharmacokinetics

Factors affecting Bioavailability of a Drug

- Pharmaceutical factors
  - These factors include the way in which a drug formulation is designed and manufactured.
- Physicochemical properties of a drug
  - Solubility of a drug in the G-I fluids - only drugs in solution can be absorbed by the G-I tract.

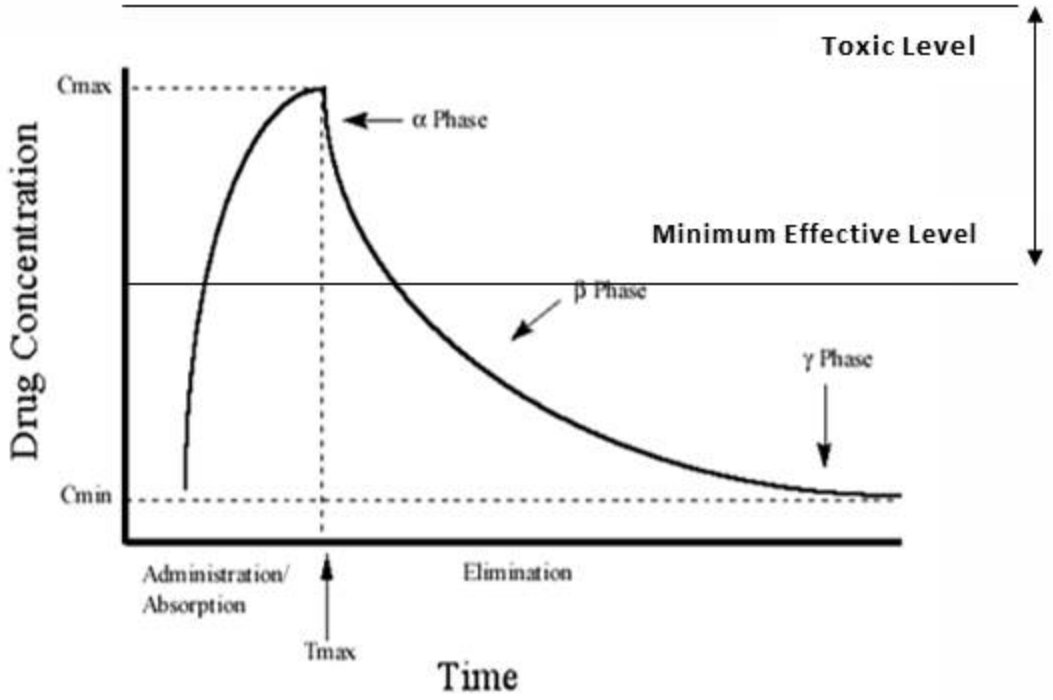
Pharmacokinetics

Factors affecting Bioavailability of a Drug (Contd)

- Factors related to the patient
  - Presence of food or other drugs in the G-I tract
  - Time taken for passing of stomach contents into the small intestine ('gastric emptying time')
  - Time duration for which the drug remains in the intestines
  - pH of the G-I tract
  - Diseases of the G-I tract

Pharmacokinetics

Estimation of Bioavailability



Time V/s Concentration curve

Pharmacokinetics

Estimation of Bioavailability (Contd)

- **Peak plasma level** (***C Max***) – the highest concentration of drug achieved in the blood circulation.
- **Time to achieve peal plasma level** (***T Max***) – time taken to achieve the highest concentration of a drug in the blood.
- **Area under curve** (***AUC***) – this represents the total amount of a drug reaching systemic circulation following administration

Pharmacokinetics

- **Minimum Effective Level** – the threshold to be crossed by the drug level in the blood in order to produce its desired effect
- **Toxic Level** – the upper limit beyond which the drug starts producing harmful effects that may be dangerous
- **Therapeutic Window** – the range of drug concentration in the blood within which the drug produces its desired effects without causing any harm to the individual

Pharmacokinetics

- **Half – Life ($t_{½}$)** – the time taken for the blood concentration (or the amount of drug in the body) to be reduced by 50 % of the previous reading
  - For example, if 500 mg is present in the body at time zero, after metabolism, 250 mg may be present at 1 h and 125 mg at 2 h illustrating a half-life of 1 h

Pharmacokinetics

Importance of half-life ($t_{½}$)

- A knowledge of half-life is required for :
  - Estimation of time required to eliminate a drug from the body after its administration is stopped
  - For deciding the dosage schedule
  - For prediction of the time required to achieve steady state plasma concentration

Pharmacokinetics

Steady State:

- Situation when the amount of drug entering the circulation equals that being removed from it
- In other words, when the blood concentration of a drug remains more or less same over a period of time, a steady state is reached
- This is seen after many doses of drug given at fixed intervals
- A steady state is achieved after approximately four to five half-lives